American Journal of Epidemiology

Vol. 160, No. 4
Printed in U.S.A.
DOI: 10.1093/aje/kwh233

Blood Transfusion and Risk of Non-Hodgkin's Lymphoma in Connecticut Women

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Received for publication September 10, 2003; accepted for publication March 24, 2004.

The incidence and mortality rates of non-Hodgkin's lymphoma have been increasing worldwide. Allogeneic blood transfusion has been suggested as a risk factor for non-Hodgkin's lymphoma, but the results from epidemiologic studies have been inconsistent. Data from a population-based case-control study of Connecticut women were analyzed to evaluate this relation. A total of 601 histologically confirmed, non-Hodgkin's lymphoma incident cases identified between 1996 and 2000 and 717 randomly selected controls were included in this study. Allogeneic blood transfusion was not associated with the increased risk of non-Hodgkin's lymphoma overall (odds ratio = 1.0, 95% confidence interval: 0.7, 1.3) or by subtype of the disease. The risk also did not vary by number of allogeneic blood transfusions, age at first transfusion, or time since first transfusion. When the reason for blood transfusion was considered, an increased risk of non-Hodgkin's lymphoma was found only for allogeneic blood transfusion for reason of anemia. In summary, the authors' findings do not support the hypothesis that allogeneic blood transfusion increases the risk of non-Hodgkin's lymphoma.

blood transfusion; Connecticut; lymphoma, non-Hodgkin; risk; women

Abbreviations: CI, confidence interval; OR, odds ratio; REAL, Revised European-American Lymphoma.

Incidence rates of non-Hodgkin's lymphoma have been increasing worldwide (1). In spite of the considerable public health significance, little is known about the etiology of non-Hodgkin's lymphoma and the causes of the observed increase in incidence rates.

The only known risk factors for non-Hodgkin's lymphoma are various primary or acquired immunosuppressions (2, 3). Allogeneic blood transfusion can induce immunosuppression (4–7) and has been suggested to increase the risk of non-Hodgkin's lymphoma. Allogeneic blood transfusion could also increase the risk of non-Hodgkin's lymphoma through engraftment of allogeneic lymphoma cells from a donor with subclinical non-Hodgkin's lymphoma (8, 9) and/or transfusion-borne oncogenic viruses (10).

Several epidemiologic studies have been conducted to investigate the relation between allogeneic blood transfusion and risk of non-Hodgkin's lymphoma. The results, however, have been inconsistent, with some suggesting an increased risk (11–14) and others reporting no association (15–20). Two studies have suggested that risk varies by specific subtype of non-Hodgkin's lymphoma (14, 21). It is also suggested that the observed association between blood transfusion and non-Hodgkin's lymphoma risk could be confounded by the underlying illnesses for which transfusions are given (22), underlining the importance of examining the association by reason for blood transfusion.

Considering that a large number of people receive blood transfusions each year worldwide and that the alleged association is uncertain, we conducted a population-based case-control study in Connecticut, one of the states with the greatest confirmed increase in the incidence of non-Hodgkin's lymphoma (23, 24), to investigate the hypothesis

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that allogeneic blood transfusion increases the risk of non-Hodgkin's lymphoma and that this risk may vary by subtype of disease.

MATERIALS AND METHODS

Study population

A detailed description of the study population has been published elsewhere (25, 26). In brief, a total of 832 histologically confirmed (*International Classification of Diseases for Oncology* (27) codes M-9590–9595, 9670–9687, 9690–9698, 9700–9723), incident non-Hodgkin's lymphoma cases were identified between 1996 and 2000 through the Yale Cancer Center's Rapid Case Ascertainment Shared Resource, an agent of the Connecticut Tumor Registry. Subjects were restricted to women who were aged 21–84 years at diagnosis, who had no previous diagnosis of cancer with the exception of nonmelanoma skin cancer, and who were alive at the time of interview. Of 832 eligible cases, 601 (72 percent) completed in-person interviews.

To provide accurate and consistent histologic classification of cases, pathology slides (or tissue blocks) were obtained from the pathology departments where the cases were diagnosed. Each specimen was independently reviewed by two study pathologists (S. F., G. T.) who are experienced in the diagnosis of lymphoma. Non-Hodgkin's lymphoma cases were classified according to both the Working Formulation and the Revised European-American Lymphoma (REAL) classification systems. The World Health Organization classification system, which is an outgrowth of the REAL classification, is utilized in both the clinical setting and epidemiologic research today. The REAL classification system was used in this paper for non-Hodgkin's lymphoma subtype analyses.

Population-based controls with Connecticut addresses were recruited using random digit dialing methods for those aged less than 65 years and Centers for Medicare and Medicaid Services' files for those aged 65 years and over. The participation rate was 69 percent for random digit dialing controls, including the initial telephone screening, and 47 percent for Centers for Medicare and Medicaid Services controls. Cases and controls were frequency matched by age in 5-year groups by adjusting the number of controls randomly selected in each age stratum every few months.

Interviews

All procedures were performed in accordance with a protocol approved by human investigation committees at Yale University, the Connecticut Department of Public Health, and the National Cancer Institute. After approval by the hospitals and by each subject's physician (for cases) or following selection through random sampling (for controls), potential participants were approached by letter and/or by phone. Those who agreed were interviewed by trained study interviewers at either the subject's home or a convenient location. A standardized, structured questionnaire was used to obtain information on blood transfusion history and other major known or suspected risk factors that might confound the association between blood transfusion and risk of non-Hodgkin's lymphoma.

Regarding blood transfusion history, subjects were asked whether they had ever had a blood transfusion during their lifetime. If so, subjects were asked to provide information regarding the year and reason for each blood transfusion they had received. For this analysis, 32 subjects who had a blood transfusion within 1 year before diagnosis or interview were considered not to have received a blood transfusion since recent blood transfusion might be related to the disease itself. Autologous blood transfusion was defined as a subject who reported having a blood transfusion using her own blood. In contrast, allogeneic blood transfusion was defined as a subject who reported having a blood transfusion without using her own blood. Only six subjects (one case and five controls) had autologous blood transfusion in this study. Thus, this paper is focused on allogeneic blood transfusion.

Information on other potential confounding factors, including family history of cancer, diet, occupation, smoking, drinking, and demographic factors, was also collected during the interview. Dietary information was collected using a scannable semiquantitative food frequency questionnaire developed and validated by the Fred Hutchinson Cancer Research Center (28, 29).

Data analysis

Unconditional logistic regression was used to estimate the association between allogeneic blood transfusion and risk of non-Hodgkin's lymphoma overall and risk of non-Hodgkin's lymphoma subtypes. The data were also analyzed according to the reason for blood transfusion and grouped into the following four categories: blood transfusion for pregnancy and/or delivery, anemia, various surgeries, and other reasons. Potential confounding variables included in the final model were age (<50, 50–70, >70 years) and family history of non-Hodgkin's lymphoma in first-degree relatives. Adjustments for other variables, such as race, education, tobacco smoking, alcohol consumption, dietary protein, and fat intake, did not result in material change of the observed associations and, thus, were not included in the final model. Odds ratios and 95 percent confidence intervals were calculated using SAS statistical software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Table 1 presents the distribution of selected characteristics for cases and controls. More cases than controls reported a family history of non-Hodgkin's lymphoma. Controls, on the other hand, had a slightly higher level of education and alcohol intake. The distribution of other factors (such as race and tobacco smoking) was quite similar between the cases and controls.

As shown in table 2, allogeneic blood transfusion was not associated with an increased risk of non-Hodgkin's lymphoma overall (odds ratio (OR) = 1.0, 95 percent confidence interval (CI): 0.7, 1.3) or by subtype of the disease. Risk was also not associated with age at first allogeneic

TABLE 1. Selected baseline characteristics of non-Hodgkin's lymphoma cases and controls, Connecticut, 1996–2000

	Cases		Controls	
	No.	%	No.	%
Age (years)				
<50	119	19.8	155	21.6
50–70	277	46.1	318	44.3
>70	205	34.1	245	34.1
Race				
White	571	95.0	668	93.0
Black	18	3.0	25	3.5
Others	12	2.0	25	3.5
Family history of non-Hodgkin's lymphoma				
No	592	98.5	714	99.4
Yes	9	1.5	4	0.6
Tobacco smoking				
No	270	44.9	323	44.9
Yes	331	55.1	395	55.1
Alcohol drinking				
No	230	38.2	233	32.5
Yes	371	61.8	485	67.5
Educational level				
High school or less	261	43.4	266	37.0
College or higher	340	56.6	452	63.0

blood transfusion on the basis of the median age among controls. The risk did not vary by number of blood transfusions or by time since first allogeneic blood transfusion (data not shown).

The results by reason for allogeneic blood transfusion are presented in table 3. Allogeneic blood transfusion for pregnancy-related complications or child delivery, surgeries, or other miscellaneous reasons was not related to the risk of non-Hodgkin's lymphoma. Allogeneic blood transfusion due to anemia, however, was associated with an increased risk overall (OR = 2.3, 95 percent CI: 0.9, 6.3) as were B-cell chronic lymphocytic leukemia (OR = 4.9, 95 percent CI: 1.2, 20.4) and T-cell lymphoma (OR = 6.2, 95 percent CI: 1.2, 32.5). Compared with those who never had a blood transfusion, women who had allogeneic blood transfusion for anemia, within 5 years or 5–10 years before diagnosis/interview, experienced an increased risk of non-Hodgkin's lymphoma (OR = 4.6, 95 percent CI: 0.5, 41.5; OR = infinity, respectively) (data not shown). Those who had allogeneic blood transfusion more than 10 years before diagnosis/interview did not experience increased risk of non-Hodgkin's lymphoma (OR = 0.9, 95 percent CI: 0.2, 3.5) (data not shown).

DISCUSSION

It is biologically plausible for allogeneic blood transfusion to increase non-Hodgkin's lymphoma risk since allogeneic blood transfusion can cause immunosupression, result in engraftment of allogeneic lymphoma cells from a donor with subclinical non-Hodgkin's lymphoma, or transfer transfusion-borne oncogenic viruses and/or chemical carcinogens (4–10). Animal models have shown that allogeneic whole blood transfusion can lead to an increase in tumor size and number of metastases (30). Epidemiologic studies, however, have provided inconsistent results linking allogeneic blood transfusion to non-Hodgkin's lymphoma risk.

Memon and Doll (11) followed 12,329 transfused infants who were identified between 1942 and 1970 through 1992, and they found that the incidence of non-Hodgkin's

TABLE 2. Allogeneic blood transfusion and risk of non-Hodgkin's lymphoma subtype by age at first blood transfusion, Connecticut, 1996–2000

Non-Hodgkin's lymphoma subtype	None			Ever				<35 years of age				≥35 years of age			
	No. of cases	No. of controls	OR*	No. of cases	No. of controls	OR†	95% CI*	No. of cases	No. of controls	OR†	95% CI	No. of cases	No. of controls	OR†	95% CI
Overall	474	560	1.0	126	152	1.0	0.7, 1.3	68	74	1.1	0.8, 1.5	58	78	0.9	0.6, 1.2
Immunologic cell type															
B-cell lymphoma	376	560	1.0	97	152	0.9	0.7, 1.3	51	74	1.0	0.7, 1.5	46	78	0.9	0.6, 1.3
T-cell lymphoma	33	560	1.0	11	152	1.3	0.6, 2.7	7	74	1.6	0.7, 3.9	4	78	0.9	0.3, 2.8
Other lymphomas	65	560	1.0	18	152	1.0	0.5, 1.7	10	74	1.1	0.6, 2.3	8	78	0.8	0.4, 1.7
REAL* classification															
BCLL*	48	560	1.0	18	152	1.2	0.7, 2.2	9	74	1.3	0.6, 2.8	9	78	1.1	0.5, 2.4
Follicular lymphoma	114	560	1.0	22	152	0.7	0.4, 1.2	14	74	0.9	0.5, 1.7	8	78	0.5	0.3, 1.2
Diffuse large B-cell lymphoma	152	560	1.0	37	152	0.9	0.6, 1.4	20	74	1.0	0.6, 1.7	17	78	0.8	0.5, 1.5
Marginal zone B-cell lymphoma	29	560	1.0	11	152	1.3	0.6, 2.8	4	74	1.0	0.4, 3.1	7	78	1.6	0.7, 3.9
Other lymphomas	131	560	1.0	38	152	1.0	0.7, 1.5	21	74	1.2	0.7, 2.0	17	78	0.9	0.5, 1.5

* OR, odds ratio; CI, confidence interval; REAL, Revised European-American Lymphoma; BCLL, B-cell chronic lymphocytic leukemia.
† Adjusted for age and family history of non-Hodgkin's lymphoma in first-degree relatives.

TABLE 3. Risks of non-Hodgkin's lymphoma based on reasons for allogeneic blood transfusion, Connecticut, 1996–2000

Non-Hodgkin's lymphoma subtype	Pregnancy/delivery				Anemia				Surgeries				Other			
	No. of cases	No. of controls	OR*,†	95% CI*	No. of cases	No. of controls	OR†	95% CI	No. of cases	No. of controls	OR†	95% CI	No. of cases	No. of controls	OR†	95% CI
Overall	53	63	1.0	0.7, 1.4	12	6	2.3	0.9, 6.3	47	72	0.8	0.5, 1.1	7	11	0.7	0.4, 1.1
Immunologic cell type																
B-cell lymphoma	42	63	1.0	0.6, 1.5	9	6	2.2	0.8, 6.4	37	72	0.8	0.5, 1.2	4	11	0.5	0.2, 1.7
T-cell lymphoma	5	63	1.4	0.5, 3.8	2	6	6.2	1.2, 32.5	3	72	0.7	0.2, 2.5	1	11	1.6	0.2, 12.8
Other lymphomas	6	63	0.8	0.3, 1.9	1	6	1.3	0.2, 11.0	7	72	0.8	0.3, 1.8	2	11	0.5	0.3, 7.0
REAL* classification																
BCLL*	8	63	1.3	0.6, 3.0	3	6	4.9	1.2, 20.4	7	72	1.0	0.4, 2.2	1	11	0.9	0.1, 7.5
Follicular lymphoma	10	63	0.8	0.4, 1.6	1	6	0.9	0.1, 7.5	9	72	0.7	0.3, 1.4	2	11	0.9	0.2, 4.2
Diffuse large B-cell lymphoma	18	63	1.1	0.6, 1.9	4	6	2.5	0.7, 9.0	11	72	0.6	0.3, 1.1	1	11	0.4	0.1, 2.7
Marginal zone B-cell lymphoma	4	63	1.2	0.4, 3.5	1	6	2.9	0.3, 25.5	4	72	1.0	0.3, 3.0	0	11		
Other lymphomas	13	63	0.9	0.6, 1.6	3	6	2.0	0.5, 8.2	16	72	0.9	0.5, 1.6	3	11	1.1	0.3, 4.1

* OR, odds ratio; CI, confidence interval; REAL, Revised European-American Lymphoma; BCLL, B-cell chronic lymphocytic leukemia.
† Adjusted for age and family history of non-Hodgkin's lymphoma in first-degree relatives.

lymphoma at age 15–49 years was about twice that expected. Blomberg et al. (12) followed 1,572 hospitalized patients with blood transfusions and reported a fourfold increase in non-Hodgkin's lymphoma mortality when compared with that of the general population. Cerhan et al. (13) reported a twofold increased risk among Iowa women followed for 5 years for the transfused group compared with the never transfused group, based on 66 cases. Two extended studies of the cohort of Iowa women reported relative risks of 1.9 (95 percent CI: 1.3, 2.8) after 7 years' follow-up based on 114 cases (31) and of 1.6 (95 percent CI: 1.2, 2.1) after 12 years' follow-up based on 229 cases (21). A major limitation of these follow-up studies is that the results were based on a relatively small number of non-Hodgkin's lymphoma cases. The Iowa women's follow-up study showed a decline in relative risk as the follow-up period and number of cases increased.

Of the several case-control studies that investigated the issue, only Brandt et al. (14) reported an excess risk of non-Hodgkin's lymphoma overall (OR = 1.7, 95 percent CI: 1.2, 2.4) and of low-grade nodal B-cell chronic lymphocytic leukemia (OR = 4.2, 95 percent CI: 1.9, 9.0) from allogeneic blood transfusion. A significantly increased risk of B-cell chronic lymphocytic leukemia associated with blood transfusion for anemia was observed in our study. In contrast, all other recently completed case-control studies have reported no increased risk of non-Hodgkin's lymphoma associated with blood transfusion (15–20). Of these, three studies that investigated the association by subtype showed no statistical significant associations between blood transfusion and specific non-Hodgkin's lymphoma subtype (17, 18, 20).

Our study does not support an association between allogeneic blood transfusion and risk of non-Hodgkin's lymphoma in Connecticut women. The risk did not vary on the basis of the number of blood transfusions received, age at first transfusion, and time since first blood transfusion. While an increased risk was observed for allogeneic blood transfusion due to anemia, no other reasons for blood transfusion were associated with the risk. An increased risk of non-Hodgkin's lymphoma associated with allogeneic blood transfusion due to anemia could be due to anemia itself, rather than blood transfusion, because anemia could result in immune impairment and is a known risk factor for non-Hodgkin's lymphoma. The observed association could also be due to the conditions that caused anemia or the subsequent medical treatments associated with anemia. The fact that increased risk was confined to those who had transfusion for anemia within 10 years before diagnosis but not in those who had transfusion more than 10 years before diagnosis may also suggest that anemia may have been an unrecognized symptom of non-Hodgkin's lymphoma. Since allogeneic blood transfusion for other causes was not associated with non-Hodgkin's lymphoma risk in our study, blood transfusion itself is unlikely to be the underlying reason for the observed increase in non-Hodgkin's lymphoma risk.

Several reasons could be used to explain the observed inconsistent results linking allogeneic blood transfusion to non-Hodgkin's lymphoma risk as reported by epidemiologic studies. One potential reason is that different studies included different types of patients with various underlying reasons for blood transfusion, as suggested by Alexander (22). The inconsistency could also be due to different treat-

ment regimens associated with underlying disease. For example, some studies may have included more transplant and transfusion patients. Immunosuppressive treatment regimens for organ-transplanted patients have been shown to increase the risk of non-Hodgkin's lymphoma (32).

Strengths and limitations should be considered in interpreting our results. The relatively large sample size with only females allows us to assess the relation by various blood transfusion characteristics, including type, age, number of blood transfusions, and time since first blood transfusion. Reported for the first time in our study is the relation by reason for allogeneic blood transfusion. The population-based incident cases were histologically confirmed by our study pathologists who are experienced in the diagnosis of lymphoma, allowing the study to analyze the relation by subtype of non-Hodgkin's lymphoma. Analysis by non-Hodgkin's lymphoma subtype is important for studies of non-Hodgkin's lymphoma, a heterogeneous group of lymphocytic disorders ranging in aggressiveness from very indolent cellular proliferation to highly aggressive and rapidly proliferative processes.

A potential limitation of our study is that the information on blood transfusion was based on subject reporting rather than on medical record review. Although it is unlikely that subjects would have had difficulty recalling having had a blood transfusion, a rare and memorable event in one's past medical history as discussed by others (22), potential bias resulting from recall of blood transfusion and the reasons for blood transfusion cannot be entirely ruled out. This is particularly true for conditions where blood transfusion may have occurred while under anesthesia or in conjunction with other kinds of fluids. Given the paucity of the studies linking blood transfusion and non-Hodgkin's lymphoma, the recall bias is more likely to be nondifferential and results in an underestimation of the observed associations.

The random digit dialing method was used to select population-based controls for those aged less than 65 years in this study. The purpose of using the random digit dialing method to select controls for those aged less than 65 years in this population-based case-control study is to use these controls to represent the population-time that produced the cases regarding exposure and other major risk factors of the disease. However, this goal may not be achieved if the coverage of telephone service is low in the source population or if a large number of randomly selected potential controls refused to participate in the study. In Connecticut, a state with comparatively high incomes, residential telephone service is widespread, with a coverage of 95 percent based on a national survey in 2000 (33). The participation rate in this study was 69 percent for random digit dialing controls, including the initial telephone screening. Moreover, since the hypothesis that allogeneic blood transfusion may induce immunosuppression and thus increase the risk of non-Hodgkin's lymphoma is not well known in the study population, and since the study participants and interviewers were not informed of the hypothesis of the study, it is unlikely that the decision to participate in the study was affected by exposure status.

In this study, subjects were restricted to women who had no previous diagnosis of cancer, with the exception of nonmelanoma skin cancer. Nonmelanoma skin cancer has been associated with the risk of non-Hodgkin's lymphoma in early epidemiologic studies (34–37). There were 39 subjects who reported having been previously diagnosed as having nonmelanoma skin cancer. Exclusion of these subjects from the analysis did not result in any material change for the observed association between blood transfusion and non-Hodgkin's lymphoma risk.

Confounding is another potential concern for the observed association between allogeneic blood transfusion for anemia and non-Hodgkin's lymphoma risk. Since we do not have information on the type of anemia and the treatment for the disease, caution must be exercised in interpreting the observed association between allogeneic blood transfusion for anemia and non-Hodgkin's lymphoma risk.

In summary, our results from this study of Connecticut women are consistent with several recently published epidemiologic studies that do not support an association between allogeneic blood transfusion and non-Hodgkin's lymphoma risk. The observed association between allogeneic blood transfusion due to anemia and non-Hodgkin's lymphoma risk may reflect the effects from the underlying disease (immune impairment due to anemia or the conditions that caused anemia), since no increased risk was observed for other causes of blood transfusion.

ACKNOWLEDGMENTS

This study is supported by grant CA62006 from the National Cancer Institute.

The authors thank the institutions that allowed access to diagnostic materials and pathology reports, including the following Connecticut hospitals: Charlotte Hungerford Hospital, Danbury Hospital, Greenwich Hospital, Griffin Hospital, Hartford Hospital, Johnson Memorial Hospital, Middlesex Hospital, Lawrence Memorial Hospital, New Britain General Hospital, Bradley Memorial Hospital, Norwalk Hospital, St. Francis Hospital and Medical Center, St. Mary's Hospital, Hospital of St. Raphael, St. Vincent's Medical Center, Stamford Hospital, William W. Backus Hospital, Waterbury Hospital, Yale-New Haven Hospital, Manchester Memorial Hospital, Rockville General Hospital, Bridgeport Hospital, Windham Hospital, Sharon Hospital, Milford Hospital, New Milford Hospital, Bristol Hospital, MidState Medical Center, and Day-Kimball Hospital. Certain data used in this study were obtained from the Connecticut Tumor Registry located in the Connecticut Department of Public Health.

The authors assume full responsibility for analyses and interpretation of these data.

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